

10/S99, 829
~~10/513699~~

Compounds

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PASSWORD:

TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * Welcome to STN International * * * * *

NEWS	1		Web Page for STN Seminar Schedule - N. America
NEWS	2	JUL 02	LMEDLINE coverage updated
NEWS	3	JUL 02	SCISEARCH enhanced with complete author names
NEWS	4	JUL 02	CHEMCATS accession numbers revised
NEWS	5	JUL 02	CA/CAPplus enhanced with utility model patents from China
NEWS	6	JUL 16	CAPplus enhanced with French and German abstracts
NEWS	7	JUL 18	CA/CAPplus patent coverage enhanced
NEWS	8	JUL 26	USPATFULL/USPAT2 enhanced with IPC reclassification
NEWS	9	JUL 30	USGENE now available on STN
NEWS	10	AUG 06	CAS REGISTRY enhanced with new experimental property tags
NEWS	11	AUG 06	BEILSTEIN updated with new compounds
NEWS	12	AUG 06	FSTA enhanced with new thesaurus edition
NEWS	13	AUG 13	CA/CAPplus enhanced with additional kind codes for granted patents
NEWS	14	AUG 20	CA/CAPplus enhanced with CAS indexing in pre-1907 records
NEWS	15	AUG 27	Full-text patent databases enhanced with predefined patent family display formats from INPADOCDB
NEWS	16	AUG 27	USPATOLD now available on STN
NEWS	17	AUG 28	CAS REGISTRY enhanced with additional experimental spectral property data
NEWS	18	SEP 07	STN AnaVist, Version 2.0, now available with Derwent World Patents Index
NEWS	19	SEP 13	FORIS renamed to SOFIS
NEWS	20	SEP 13	INPADOCDB enhanced with monthly SDI frequency
NEWS	21	SEP 17	CA/CAPplus enhanced with printed CA page images from 1967-1998
NEWS	22	SEP 17	CAPplus coverage extended to include traditional medicine patents
NEWS	23	SEP 24	EMBASE, EMBAL, and LEMBASE reloaded with enhancements
NEWS EXPRESS	19	SEPTEMBER 2007: CURRENT WINDOWS VERSION IS V8.2, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 19 SEPTEMBER 2007.	
NEWS HOURS	STN Operating Hours Plus Help Desk Availability		
NEWS LOGIN	Welcome Banner and News Items		
NEWS IPC8	For general information regarding STN implementation of IPC 8		

Enter NEWS followed by the item number or name to see news on that specific topic.

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* * * * * STN Columbus * * * * *

FILE 'HOME' ENTERED AT 16:41:51 ON 24 SEP 2007

=> file reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 16:41:58 ON 24 SEP 2007

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<http://www.cas.org/support/stngen/stndoc/properties.html>

=>

Uploading C:\Program Files\Stnexp\Queries\10599824.str

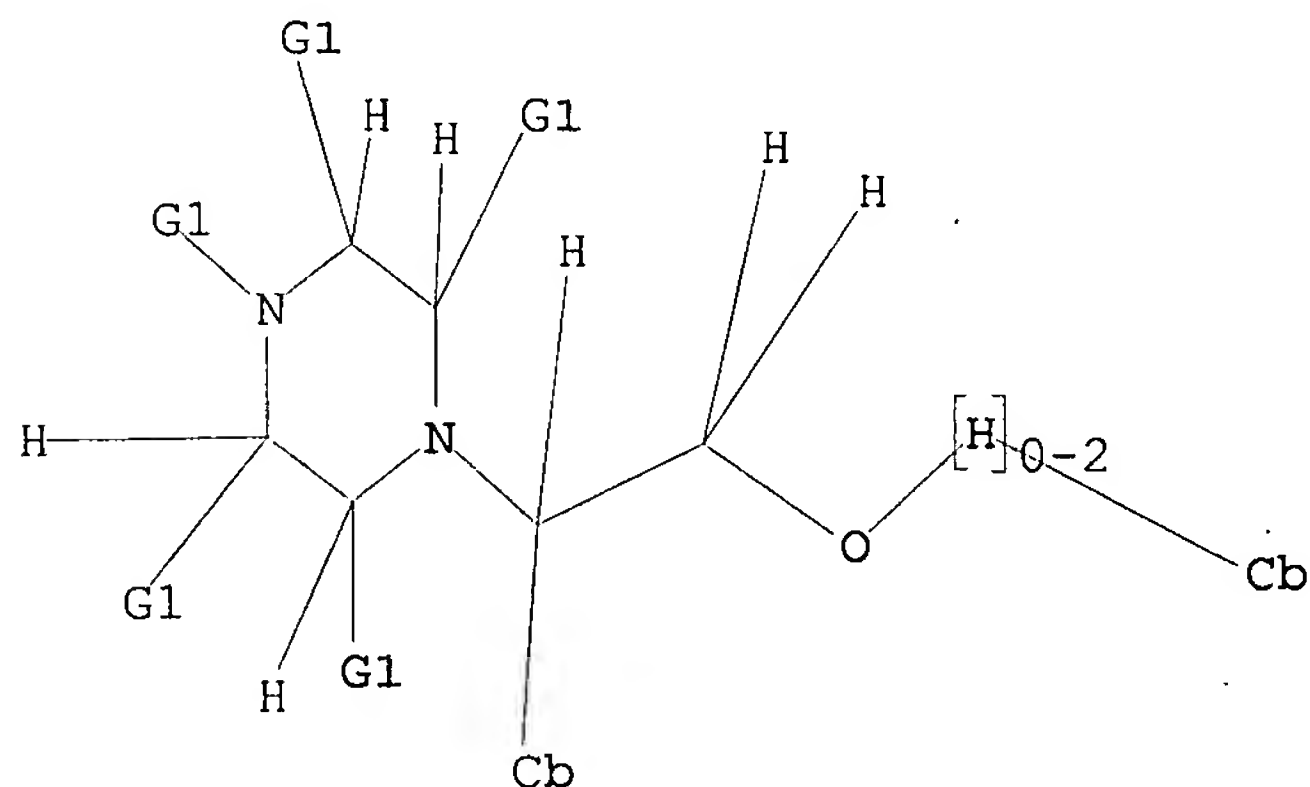
L1 STRUCTURE UPLOADED

=> d l1

L1 HAS NO ANSWERS

L1 STR

10/513699



G1 H,X,Ak,O

Structure attributes must be viewed using STN Express query preparation.

=> s l1 full
FULL SEARCH INITIATED 16:42:20 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 258294 TO ITERATE

100.0% PROCESSED 258294 ITERATIONS 1 ANSWERS
SEARCH TIME: 00.00.04

L2 1 SEA SSS FUL L1

=> file caplus		
COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	172.10	172.31

FILE 'CAPLUS' ENTERED AT 16:42:31 ON 24 SEP 2007
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FILE COVERS 1907 - 24 Sep 2007 VOL 147 ISS 14
FILE LAST UPDATED: 23 Sep 2007 (20070923/ED)

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<http://www.cas.org/infopolicy.html>

<12/04/2007>

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10/513699

=> s 11 full

REGISTRY INITIATED

Substance data SEARCH and crossover from CAS REGISTRY in progress...

Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.

FULL SEARCH INITIATED 16:42:39 FILE 'REGISTRY'

FULL SCREEN SEARCH COMPLETED - 258294 TO ITERATE

100.0% PROCESSED 258294 ITERATIONS

1 ANSWERS

SEARCH TIME: 00.00.04

L3 1 SEA SSS FUL L1

L4 1 L3

=> file caplus

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

0.47

345.35

FILE 'CAPLUS' ENTERED AT 16:42:49 ON 24 SEP 2007

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=> s 12 full

L5 1 L2

=> d ibib abs

L5 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:589533 CAPLUS

DOCUMENT NUMBER: 141:140464

TITLE: N-(substituted arylmethyl)-4-(disubstituted

<12/04/2007>

Erich Leese

methy)l)piperidines and piperazines

INVENTOR(S): Ding, Ping; Henrie, Robert N., II; Cohen, Daniel H.;
Lyga, John W.; Rosen, David S.; Theodoridis, George;
Zhang, Qun; Yeager, Walter H.; Donovan, Stephen F.;
Zhang, Steven Shunxiang; Shulman, Inna; Yu, Seong Jae;
Wnag, Gouzhi; Zhang, Y. Larry; Gopalsamy, Ariamala;
Warkentin, Dennis L.; Rensner, Paul E.; Silverman, Ian
R.; Cullen, Thomas G.

PATENT ASSIGNEE(S): FMC Corporation, USA

SOURCE: PCT Int. Appl., 105 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

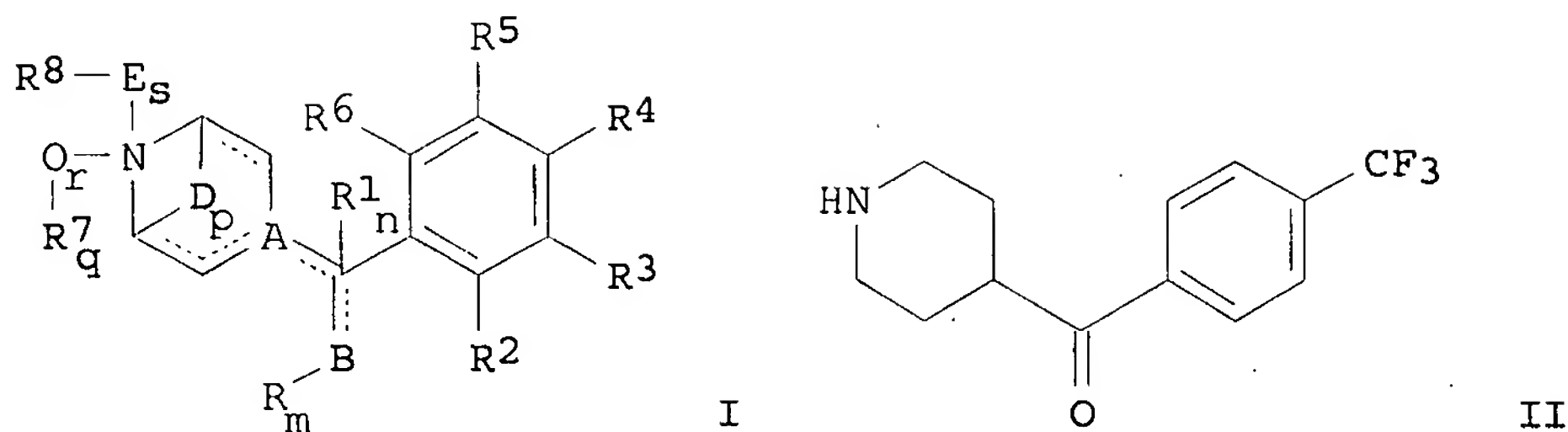
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004060865	A2	20040722	WO 2003-US39046	20031208
WO 2004060865	A3	20041104		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
AU 2003296373	A1	20040729	AU 2003-296373	20031208
EP 1572668	A2	20050914	EP 2003-814673	20031208
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK			
BR 2003016747	A	20051018	BR 2003-16747	20031208
CN 1729178	A	20060201	CN 2003-80106750	20031208
CN 1744895	A	20060308	CN 2003-80109445	20031208
JP 2006511621	T	20060406	JP 2005-508564	20031208
IN 2005DN02489	A	20061229	IN 2005-DN2489	20050609
IN 2005DN02485	A	20070427	IN 2005-DN2485	20050609
ZA 2005004870	A	20060426	ZA 2005-4870	20050614
ZA 2005004871	A	20060426	ZA 2005-4871	20050614
MX 2005PA06426	A	20050908	MX 2005-PA6426	20050615
US 2006166962	A1	20060727	US 2006-538997	20060208
PRIORITY APPLN. INFO.:			US 2002-434718P	P 20021218
			US 2003-495059P	P 20030814
			WO 2003-US39046	W 20031208
OTHER SOURCE(S):	MARPAT 141:140464			
GI				

10/513699



AB Title compds. I [m, n, q, r, s = 0-1; p = 0-3; A = CH, N forming a 6-membered azine ring selected from piperidine or piperazine; R2-6 = H, halo, alkyl, etc.; B = O; with provisions] are prepared For instance, 4-bromobenzotrifluoride is transmetalated (THF, n-BuLi, -75°) and treated with tert-Bu 4-[N-methoxy-N-methylcarbamoyl]piperidine-1-carboxylate to give tert-Bu 4-[(4-(trifluoromethyl)phenyl)carbonyl]piperidine-1-carboxylate. This intermediate is deprotected to give II. II gave 100% mortality and 100% growth inhibition of tobacco budworms.

=> d hitstr

L5 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2007 ACS on STN

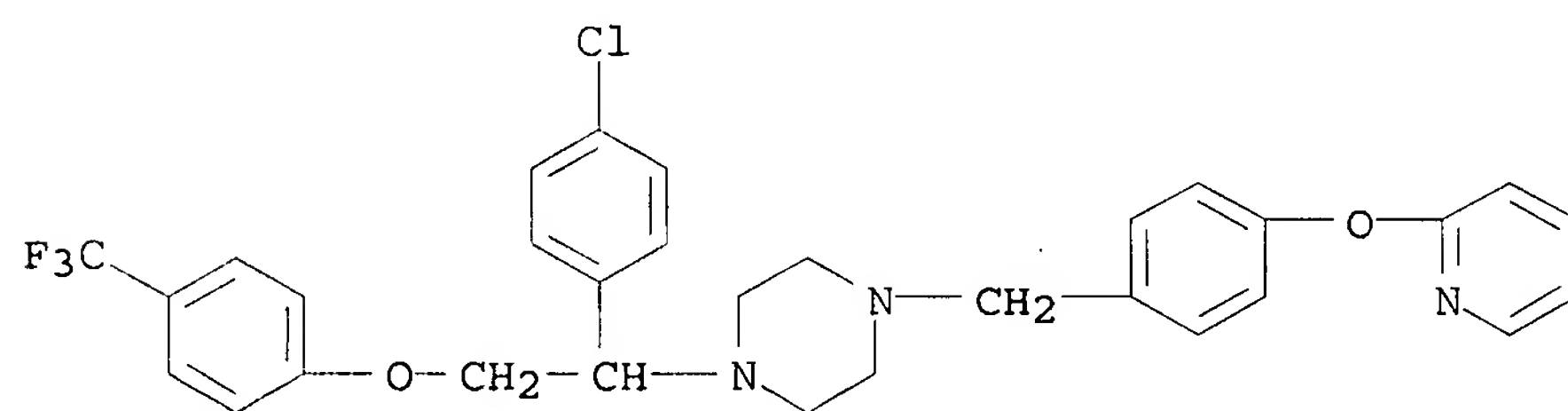
IT 725231-94-7P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(N-(substituted arylmethyl)-4-(disubstituted methyl)piperidines and piperazines)

RN 725231-94-7 CAPLUS

CN Piperazine, 1-[1-(4-chlorophenyl)-2-[4-(trifluoromethyl)phenoxy]ethyl]-4-[[4-(2-pyridinyloxy)phenyl]methyl]- (9CI) (CA INDEX NAME)



=> file reg

COST IN U.S. DOLLARS

SINCE FILE
ENTRY

TOTAL
SESSION

FULL ESTIMATED COST

8.56

353.91

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE
ENTRY

TOTAL
SESSION

CA SUBSCRIBER PRICE

-0.78

-0.78

FILE 'REGISTRY' ENTERED AT 16:47:02 ON 24 SEP 2007

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DICTIONARY FILE UPDATES: 23 SEP 2007 HIGHEST RN 947726-74-1

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<http://www.cas.org/support/stngen/stndoc/properties.html>

=>

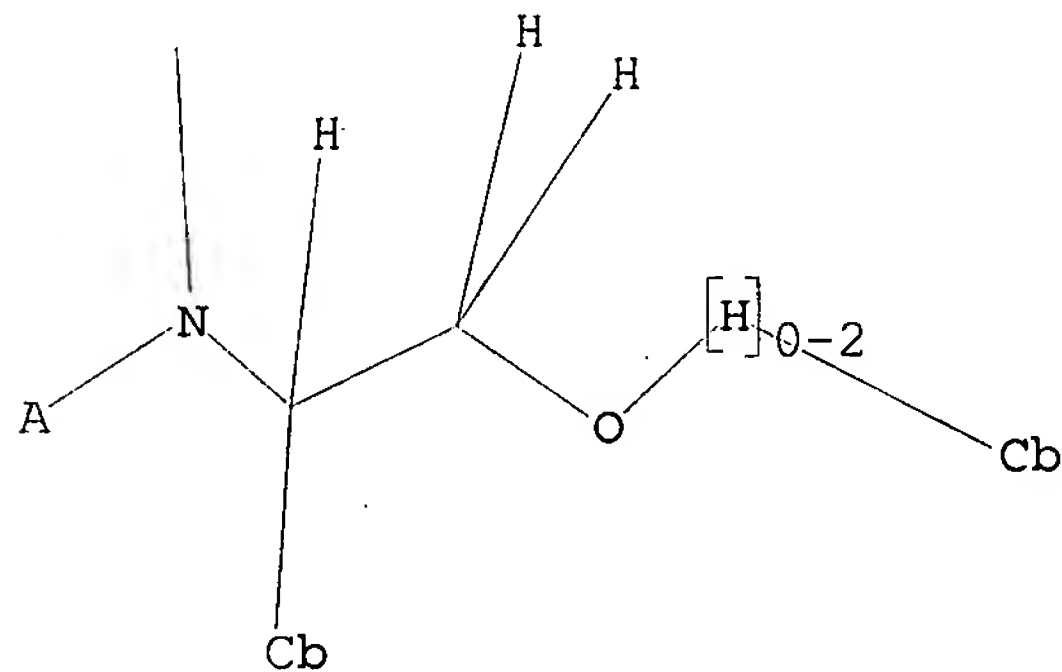
Uploading C:\Program Files\Stnexp\Queries\10599824broad.str

L6 STRUCTURE UPLOADED

=> d l6

L6 HAS NO ANSWERS

L6 STR



G1 H, X, Ak, O

Structure attributes must be viewed using STN Express query preparation.

=> s l6 full

FULL SEARCH INITIATED 16:50:46 FILE 'REGISTRY'

FULL SCREEN SEARCH COMPLETED - 6037621 TO ITERATE

8.6% PROCESSED	516823 ITERATIONS	7 ANSWERS
15.8% PROCESSED	955056 ITERATIONS	7 ANSWERS
16.6% PROCESSED	1000000 ITERATIONS	7 ANSWERS

<12/04/2007>

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10/513699

INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.39

FULL FILE PROJECTIONS: ONLINE **INCOMPLETE**
BATCH **INCOMPLETE**
PROJECTED ITERATIONS: 6037621 TO 6037621
PROJECTED ANSWERS: 23 TO 61

L7 7 SEA SSS FUL L6

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	175.25	529.16
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-0.78

FILE 'CAPLUS' ENTERED AT 16:51:32 ON 24 SEP 2007
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FILE LAST UPDATED: 23 Sep 2007 (20070923/ED)

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=> s l7 full

L8 2 L7

=> d ibib abs hitstr tot

L8 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:908614 CAPLUS
DOCUMENT NUMBER: 145:454704
TITLE: Effect of the Phosphoryl Substituent in the Linear Nitron on the Spin Trapping of Superoxide Radical and the Stability of the Superoxide Adduct: Combined Experimental and Theoretical Studies
AUTHOR(S): Liu, Yang-Ping; Wang, Lan-Fen; Nie, Zhou; Ji, Yi-Qiong; Liu, Yang; Liu, Ke-Jian; Tian, Qiu
CORPORATE SOURCE: State Key Laboratory for Structural Chemistry of Unstable and Stable Species, Center for Molecular

<12/04/2007>

Erich Leese

Science, Institute of Chemistry, Chinese Academy of Sciences, Beijing, 100080, Peop. Rep. China

SOURCE: Journal of Organic Chemistry (2006), 71(20), 7753-7762
CODEN: JOCEAH; ISSN: 0022-3263

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

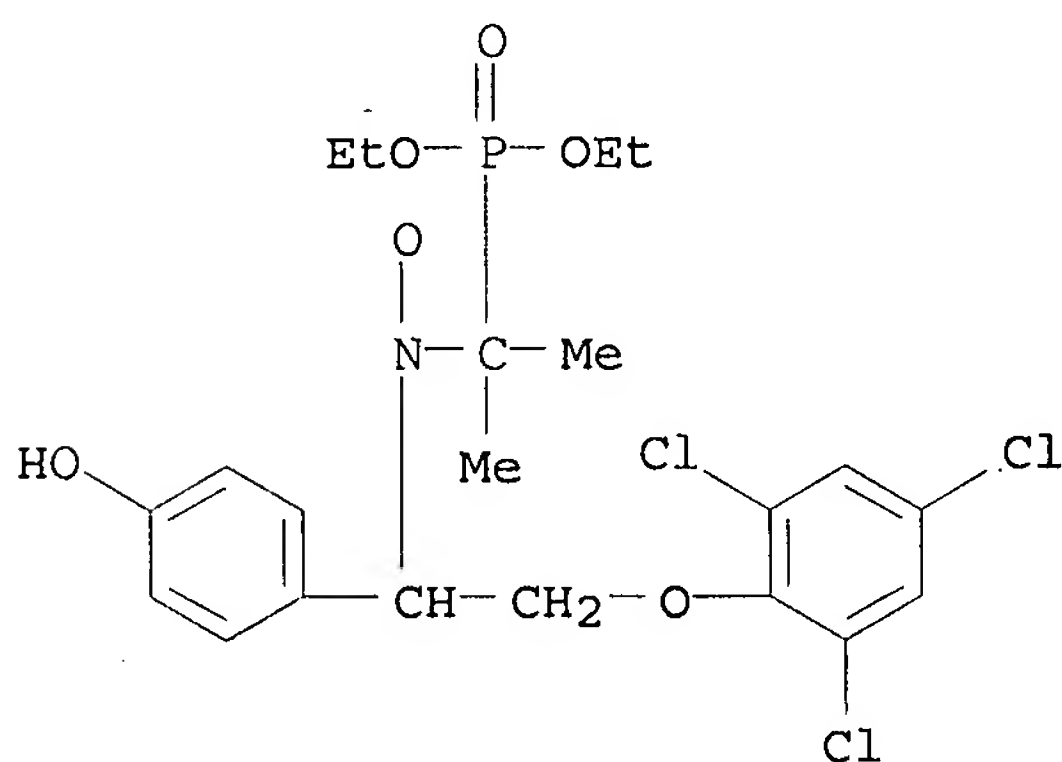
OTHER SOURCE(S): CASREACT 145:454704

AB A new phosphorylated linear nitron N-(4-hydroxybenzylidene)-1-diethoxyphosphoryl-1-methylethylamine N-oxide (4-HOPPN) was synthesized, and its X-ray structure was determined. The spin trapping ability of various kinds of free radicals by 4-HOPPN was evaluated. Kinetic study of decay of the superoxide spin adduct (4-HOPPN-OOH) shows the half-life time of 8.8 min. On the basis of the X-ray structural coordinates, theor. analyses using d. functional theory (DFT) calcns. at the B3LYP/6-31+G(d,p)//B3LYP/6-31G(d) level were performed on spin-trapping reactions of superoxide radical with 4-HOPPN and PBN and three possible decay routes for their corresponding superoxide adducts. The comparative calcns. on the spin-trapping reactions with superoxide radical predicted that both spin traps share an identical reaction type and have comparable potency when spin trapping superoxide radical. Anal. of the optimized geometries of 4-HOPPN-OOH and PBN-OOH reveals that an introduction of the phosphoryl group can efficiently stabilize the spin adduct through the intramol. H-bonds, the intramol. nonbonding attractive interactions, as well as the bulky steric protection. Examination of the decomposition thermodyn. of 4-HOPPN-OOH and PBN-OOH further supports the stabilizing role of the phosphoryl group to a linear phosphorylated spin adduct.

IT 913260-59-0
RL: FMU (Formation, unclassified); PRP (Properties); FORM (Formation, nonpreparative)
(effect of phosphoryl substituent in linear nitron on spin trapping of superoxide radical and stability of superoxide)

RN 913260-59-0 CAPLUS

CN Nitroxide, 1-(diethoxyphosphinyl)-1-methylethyl 1-(4-hydroxyphenyl)-2-(2,4,6-trichlorophenoxy)ethyl (9CI) (CA INDEX NAME)



REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:874491 CAPLUS

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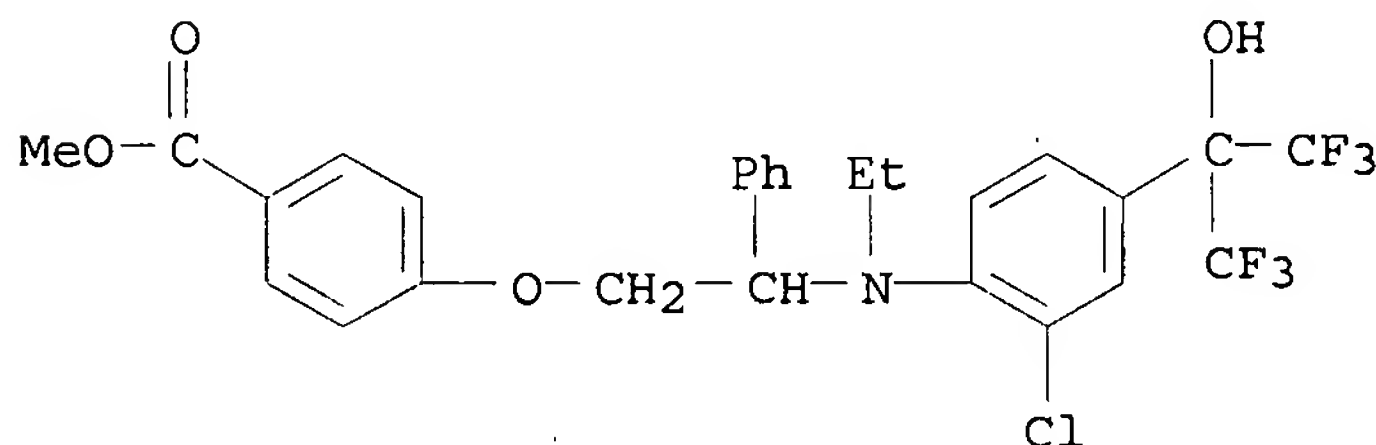
DOCUMENT NUMBER: 145:471200
TITLE: Synthesis and evaluation of
anilinohexafluoroisopropanols as activators/modulators
of LXR α and β
AUTHOR(S): Panday, Narendra; Benz, Jorg; Blum-Kaelin, Denise;
Bourgeaux, Vanessa; Dehmlow, Henrietta; Hartman,
Peter; Kuhn, Bernd; Ratni, Hassen; Warot, Xavier;
Wright, Matthew B.
CORPORATE SOURCE: Pharmaceuticals Division, Preclinical Research, F.
Hoffmann-La Roche Ltd., Basel, CH-4070, Switz.
SOURCE: Bioorganic & Medicinal Chemistry Letters (2006),
16(19), 5231-5237
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 145:471200

AB A series of branched and unbranched anilinohexafluoroisopropanols related to the known sulfonamide T0901317 were prepared and evaluated as activators/modulators of both LXR α and LXR β . A structure-activity relationship was established and compds. with high potency on both the receptors were identified. Many compds. showed a tendency toward selectivity for LXR β vs. LXR α . Several analogs were evaluated for effects on plasma lipoprotein levels in mice. A few of these significantly raised HDL-cholesterol levels in plasma but showed markedly different effects on liver triglyceride content, suggesting that this series may yield candidates with improved efficacy/safety profiles compared to existing mols.

IT 913619-59-7P 913619-60-0P 913619-61-1P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and evaluation of anilinohexafluoroisopropanols as activators/modulators of LXR α and β)

RN 913619-59-7 CAPLUS

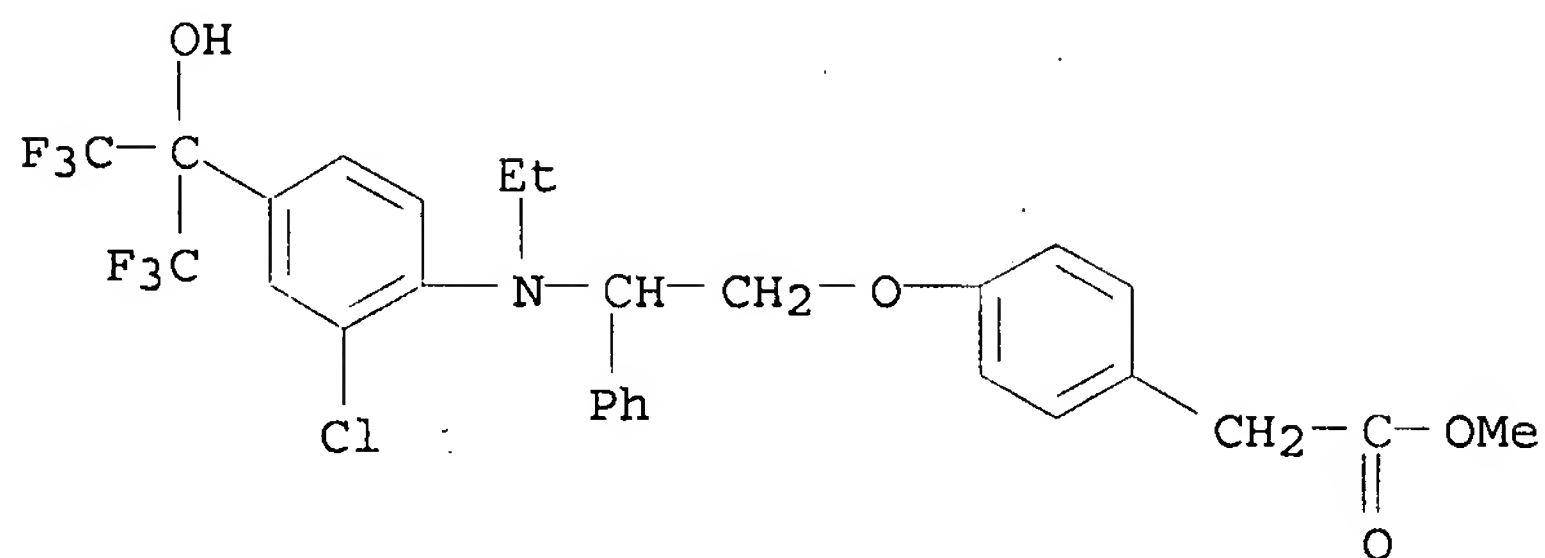
CN Benzoic acid, 4-[2-[[2-chloro-4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]ethylamino]-2-phenylethoxy]-, methyl ester
(CA INDEX NAME)



RN 913619-60-0 CAPLUS

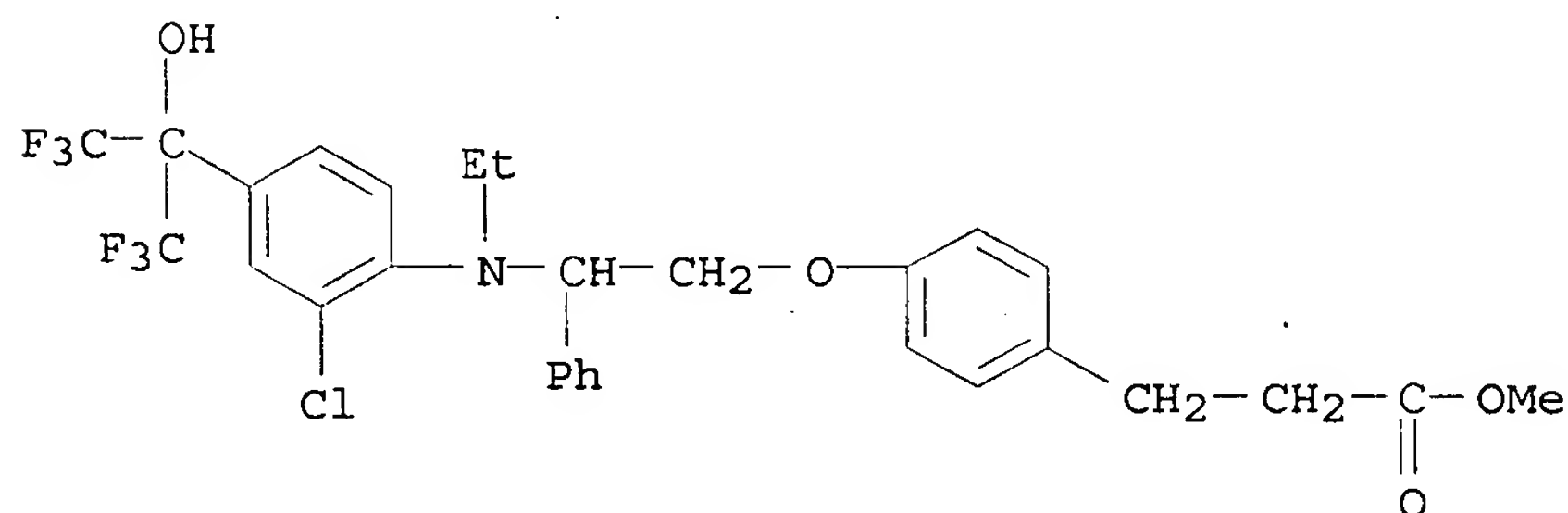
CN Benzeneacetic acid, 4-[2-[[2-chloro-4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]ethylamino]-2-phenylethoxy]-, methyl ester
(CA INDEX NAME)

10/513699



RN 913619-61-1 CAPLUS

CN Benzenepropanoic acid, 4-[2-[[2-chloro-4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]ethylamino]-2-phenylethoxy]-, methyl ester (CA INDEX NAME)

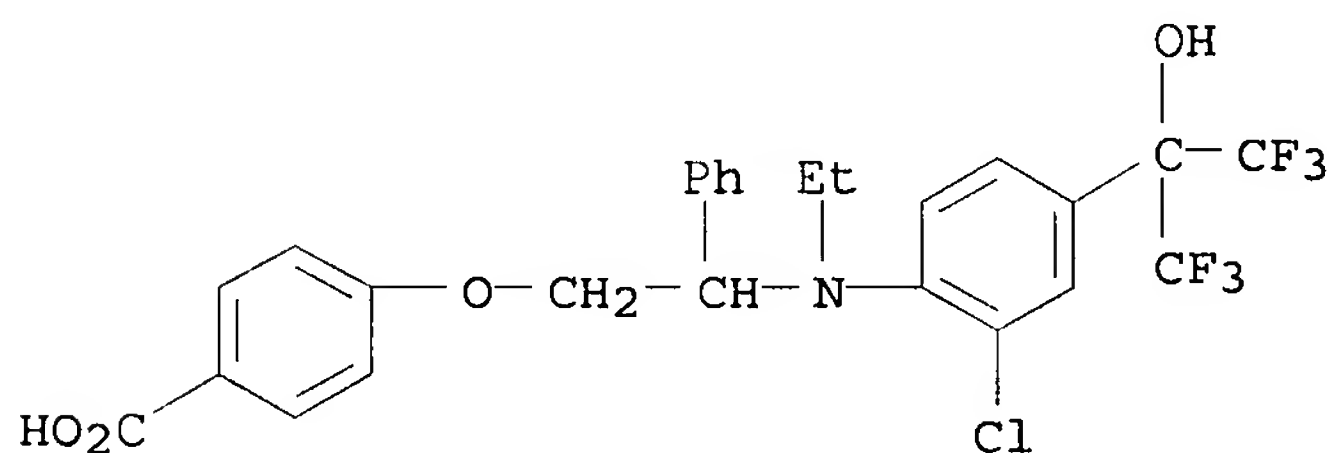


IT 913619-62-2P 913619-63-3P 913619-64-4P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis and evaluation of anilinohexafluoroisopropanols as activators/modulators of LXR α and β)

RN 913619-62-2 CAPLUS

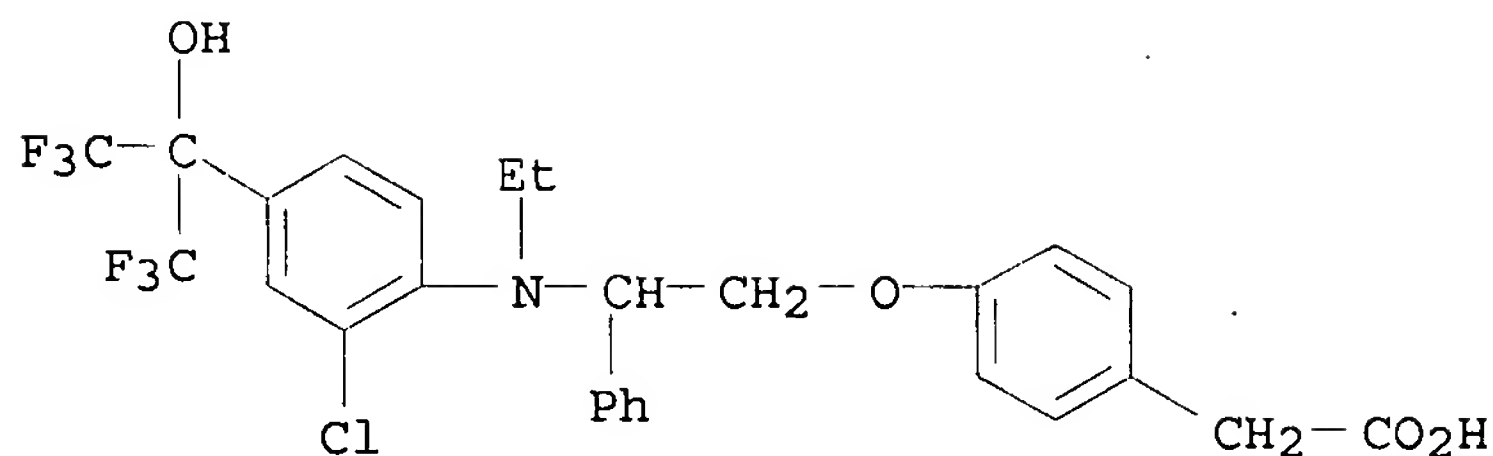
CN Benzoic acid, 4-[2-[[2-chloro-4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]ethylamino]-2-phenylethoxy]- (CA INDEX NAME)



RN 913619-63-3 CAPLUS

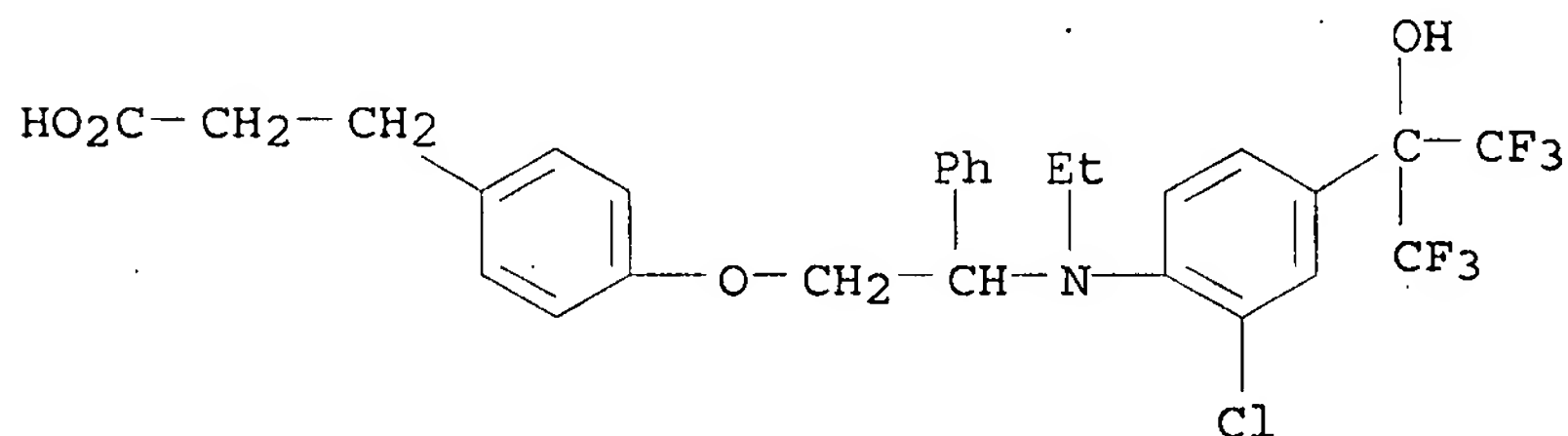
CN Benzeneacetic acid, 4-[2-[[2-chloro-4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]ethylamino]-2-phenylethoxy]- (CA INDEX NAME)

10/513699



RN 913619-64-4 CAPLUS

CN Benzenepropanoic acid, 4-[2-[[2-chloro-4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]ethylamino]-2-phenylethoxy]- (CA INDEX NAME)



REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> file reg

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

12.89

542.05

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE

TOTAL

ENTRY

SESSION

CA SUBSCRIBER PRICE

-1.56

-2.34

FILE 'REGISTRY' ENTERED AT 16:54:45 ON 24 SEP 2007

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STRUCTURE FILE UPDATES: 23 SEP 2007 HIGHEST RN 947726-74-1

DICTIONARY FILE UPDATES: 23 SEP 2007 HIGHEST RN 947726-74-1

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<12/04/2007>

Erich Leese

10/513699

experimental property data in the original document. For information on property searching in REGISTRY, refer to:

<http://www.cas.org/support/stngen/stndoc/properties.html>

=>

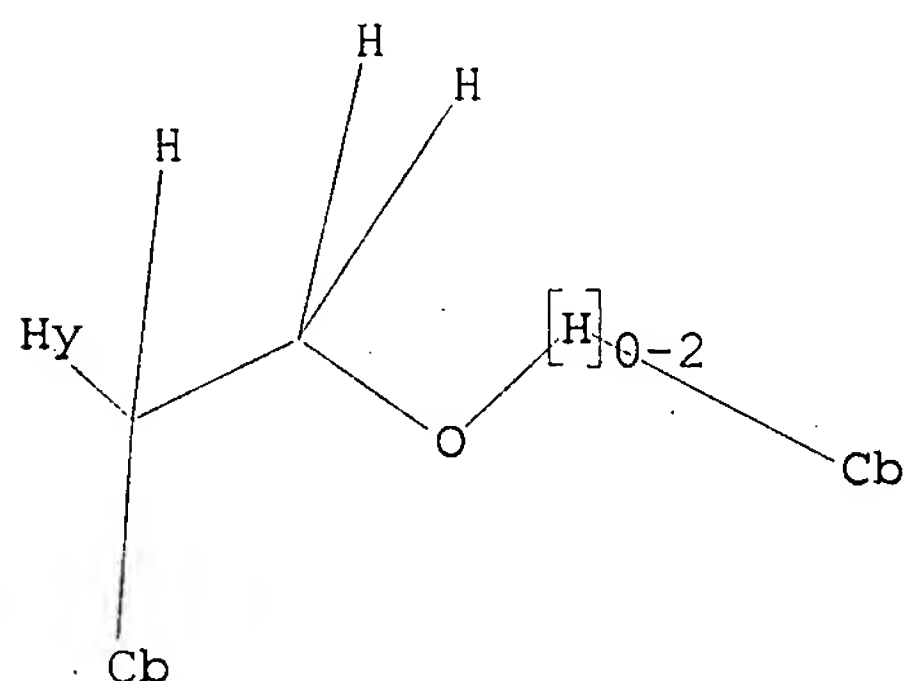
Uploading C:\Program Files\Stnexp\Queries\10599824last.str

L9 STRUCTURE UPLOADED

=> d l9

L9 HAS NO ANSWERS

L9 STR



G1 H, X, Ak, O

Structure attributes must be viewed using STN Express query preparation.

=> s l9 full

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Dual NK₁ Antagonists—Serotonin Reuptake Inhibitors as Potential Antidepressants. Part 2: SAR and Activity of Benzyloxyphenethyl Piperazine Derivatives[†]

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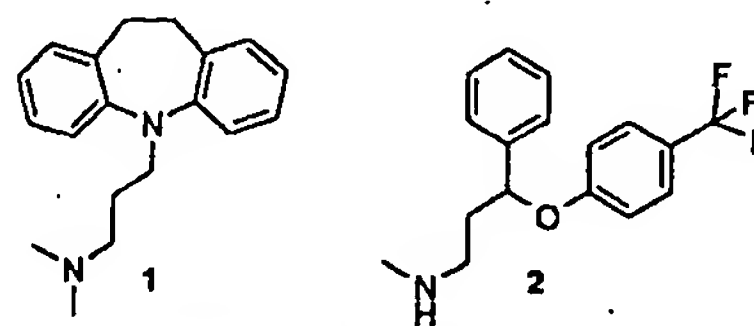
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Abstract—The synthesis, structure–affinity relationship and activity of benzyloxyphenethyl piperazine derivatives combining NK₁ antagonism and serotonin reuptake inhibition is described. Compound 7u was shown to be active in animal models of 5-HT reuptake inhibition and central NK₁ receptor blockade, and was demonstrated to be orally active in an integrated model sensitive to both mechanisms. This class of compounds potentially represents a new generation of antidepressants.
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Depression is reported to affect up to 10% of the population² and is linked with a significant mortality. Antidepressant therapies using tricyclics (such as imipramine 1) or Selective Serotonin Reuptake Inhibitors (SSRIs) such as fluoxetine 2 are efficacious in about 70% of patients but are associated with side effects such as dry mouth and blurred vision for tricyclics, and gastrointestinal distress, anxiety, insomnia and sexual dysfunction for the SSRIs.

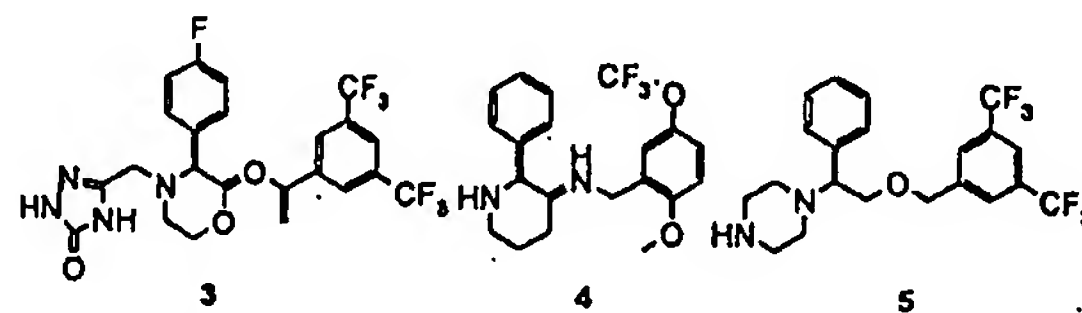
Another common problem in current therapies is their slow onset of action, since a delay of about 4 weeks is normally observed between the beginning of the treatment and alleviation of the symptoms. This delay appears to parallel the progressive desensitization of somatodendritic 5HT_{1A} receptors which in turn gradually increases serotonergic function. Indeed, clinical evidence shows that co-administration of a 5-HT_{1A} antagonist such as pindolol has a beneficial effect on the onset of action of SSRIs.^{3,4}

Several lines of research^{4,5} are being pursued along these lines for the discovery of new antidepressants, as well as non-monoaminergic approaches such as estrogen,^{6,7} CRF^{8–14} and NK₁¹⁵ receptor ligands (Scheme 1).



Scheme 1. First- and second-generation antidepressants.

Thus far, NK₁ antagonists^{15–18} seem especially promising. Indeed, in an animal model of depression,¹⁹ NK₁ antagonists have a faster onset of action than imipramine (1). In clinical trials, two NK₁ antagonists, MK-869¹⁶ (3) and CP 122,721^{20,21} (4) were reported to have robust efficacy in treating depression (Scheme 2).



Scheme 2. NK₁ antagonists: MK-869, CP 122,721 and compound 5.

[†]For Part I, see ref 1.

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The mode of action of NK₁ antagonists is now believed to involve an indirect modulation of 5-HT function, via Noradrenergic pathways.^{22,23} NK₁ receptor knock-out mice and wild-type mice treated with NK₁ antagonists have an attenuated presynaptic 5HT_{1A} receptor function.^{23–25} The combination of serotonin reuptake inhibition with NK₁ antagonism (modulating 5HT_{1A} function) may thus lead to a new class of antidepressants with an improved onset of action and better efficacy.

The optimisation of a family of phenoxyacetamides with dual affinities for the NK₁ receptor and the Serotonin Reuptake Site has recently been reported,¹ while Merck has described in the patent literature compounds claimed to have a similar profile.²⁶ We now report the SAR and in vivo activity of benzyloxyphenethyl piperazine derivatives that similarly combine Serotonin Reuptake Inhibition and NK₁ antagonism.

Screening^{27–29} of NK₁ antagonists from the UCB compound collection against the Serotonin Transporter (ST) resulted in the identification, amongst others, of compound 5 (Table 1), which displays excellent affinity for the NK₁ receptor but moderate affinity for the ST. This compound was used as a starting point for this work.

Chemistry

The key alcohols 6 were prepared by either substitution of a bromo phenylacetic ester with the Boc-protected piperazine followed by reduction, or by an efficient,

Table 1. Affinities of compounds 2–7 for the NK₁ receptor and the Serotonin Transporter (ST)

Compd (configuration)	R ₁	R ₂	pIC ₅₀ NK ₁ ^a	pIC ₅₀ ST ^a
2 fluoxetine	—	—	— ^b	8.2
3 MK 869	—	—	10.0 ^c	—
5	—	3', 5'-di CF ₃	8.3	6.6
7a	4-F	3', 5'-di CF ₃	7.0	6.8
7b	4-OMe	3', 5'-di CF ₃	7.3	7.0
7c	3-Cl	3', 5'-di CF ₃	8.8	6.6
7d	3-iPr	3', 5'-di CF ₃	7.4	6.5
7e	3-OMe	3', 5'-di CF ₃	9.0	6.7
7f	2-F	3', 5'-di CF ₃	8.3	6.7
7g	2-Cl	3', 5'-di CF ₃	8.8	6.7
7h	2-OMe	3', 5'-di CF ₃	8.2	6.6
7i	3,4-di Cl	3', 5'-di CF ₃	8.3	6.7
7j	2,3-di F	3', 5'-di CF ₃	8.5	6.5
7k	—	3', 5'-di Me	7.6	— ^d
7l	—	3', 5'-di ^t Bu	7.0	6.0
7m	—	3'-Cl	6.4	8.1
7n	—	3', 5'-di F	6.7	9.1
7o	—	3'-CF ₃ , 5'-F	7.9	7.8
7p	—	3'-Br, 5'-I	8.9	7.6
7q	—	1'-OMe, 3', 5'-di Br	8.1	8.2
7r (R)	—	3', 5'-di Cl	7.6	7.9
7s (S)	—	3', 5'-di Cl	8.5	8.6
7t (R)	—	3', 5'-di Br	7.9	7.5
7u (S)	—	3', 5'-di Br	8.5	8.0

^aValues are means of two experiments.

^bLess than 50% inhibition at 10^{−5} M.

^cSee ref 32.

^dNot tested.

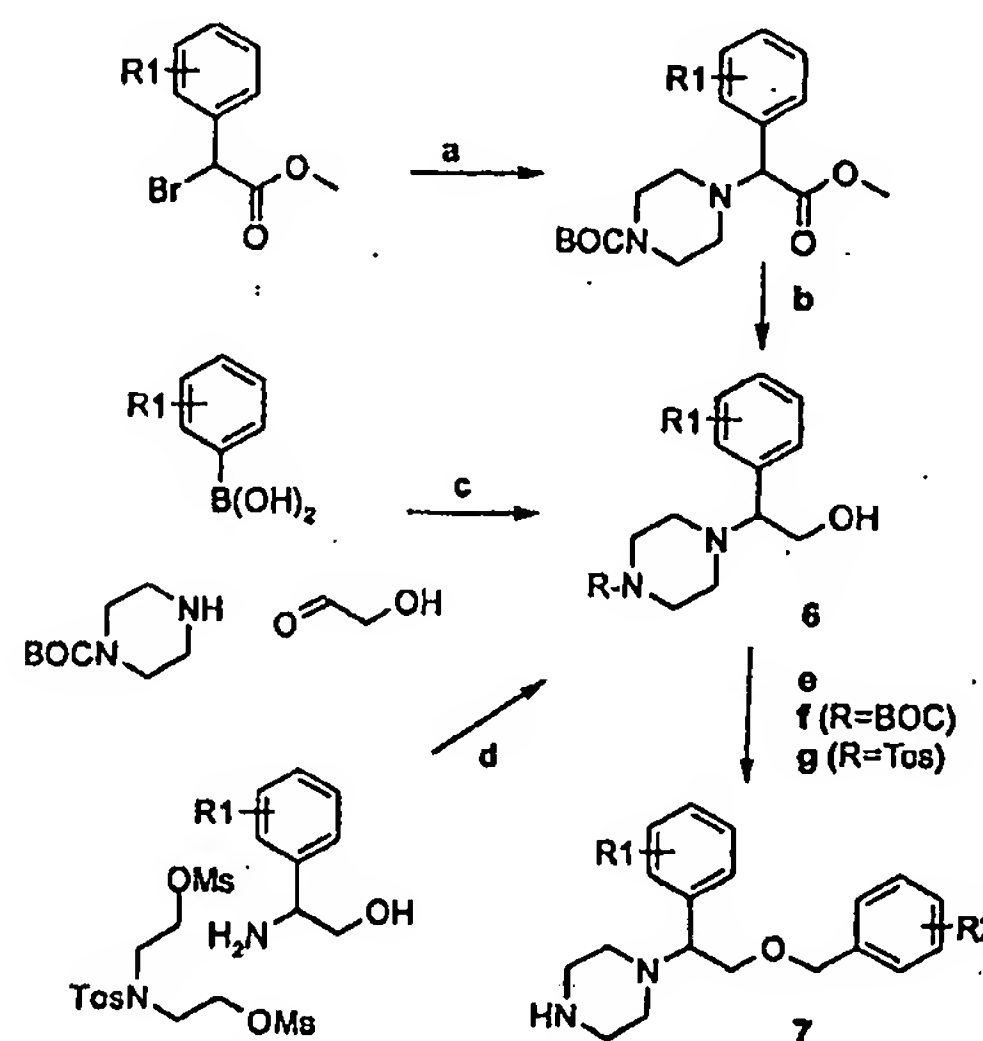
three component reaction^{30,31} between an arylboronic acid, glycolaldehyde and the Boc-protected piperazine. Enantiopure 6 were prepared by reaction of homochiral phenylglycinols with the activated *N*-tosyl diethanolamine derivative. Alcohols 6 were then *O*-benzylated and deprotected to afford the corresponding compounds 7 in racemic (7a–q) or enantiopure (7r–u) form (Scheme 3).

Results

Modification of R₁ while keeping R₂ substitution constant showed that the NK₁ receptor does not tolerate 4-substituents while affinities for the ST were slightly improved (7a, 7b). Substitution of the 3-position with chloro- or methoxy- was beneficial to NK_{1r} binding (7c, 7e) but affinities for the ST were unaffected. Finally 2-substitution with a chloro group (7g) was found to improve affinities for the NK_{1r} but again left affinities for the ST unchanged. 3,4- and 2,3-Disubstitutions were not beneficial (7i, 7j). We then turned to modification of R₂ in order to improve affinity for the ST.

Substitution with small (7k) or large (7l) alkyl groups led to an overall loss of affinities. Monosubstitution (7m) or disubstitution with the smaller fluoro atoms (7n) led to an important reduction of the affinities toward NK_{1r} while ST binding was greatly improved. Unsymmetrical disubstitution with the 3'-CF₃, 5'-F (7o) or 3'-bromo 5'-iodo (7p) provided compounds with high affinities for both targets. Trisubstitution (7q) was also beneficial.

At this stage, enantiopure compounds bearing the 3',5'-dichloro and 3',5'-dibromo substitution (7r–7u) were prepared. Fortunately, in each case, the *S* enantiomers displayed very high affinities toward both targets, while



Scheme 3. Preparation of benzyloxyphenethyl piperazines: (a) Boc-piperazine, K₂CO₃, DMF, rt; (b) LiBH₄, THF, reflux; (c) CH₂Cl₂, rt; (d) Et₃N, DMF, 80 °C; (e) NaH, THF, Benzyl bromide, NaI, 60 °C; (f) TFA-CH₂Cl₂; (g) AcOH-HBr, 90 °C.

102(b)

the *R* enantiomers proved to be inferior. Compounds 7s and 7u were selected for further examination in vivo.

To assess the central 5-HT reuptake blockade properties of the compounds, we tested their ability to increase extracellular 5-HT levels in the frontal cortex of freely moving rats by using intracerebral microdialysis.³³ Intraperitoneal administration of 7u (3.2×10^{-5} mol/kg, $n=2$) increased 5-HT levels up to 250% of baseline for more than 3 h. In this model, 7s was found to be poorly active, possibly because of metabolic instability or limited brain penetration. Activity of 7u as a NK₁ antagonist was assessed using the gerbil foot-tapping model as described by Rupniak.³⁴ At the dose of 3.2×10^{-5} mol/kg (ip, $n=5$), 7u decreased by 45% the duration of the foot-tapping, indicating efficacious central blockade of NK₁ receptors. Finally, in the isolation-induced guinea pig pup vocalization test, an integrated behavioural model sensitive to both SSRI and NK₁ antagonists,³⁵ 7u was shown to be orally active, as it was able to attenuate by 50% (1×10^{-5} mol/kg, $n=8$) and 99% (3.5×10^{-5} mol/kg, $n=8$) the duration of vocalizations.

In conclusion, we were able to optimise a family of benzyloxyphenethyl piperazines to the level of fluoxetine for the ST, with an added affinity for the NK₁ receptor. One of the best compounds in this family was shown to be active in animal models indicative of 5-HT reuptake inhibition and central NK₁ receptor blockade, and was demonstrated to be orally active in an validated animal model of depression sensitive to both mechanisms.

Further developments in this area will be reported in due course.

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